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EXAMINER	
SKOWRONEK, KARLHEINZ R	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/559,899	VAN MARCK ET AL.	
	Examiner	Art Unit	
	KARLHEINZ R. SKOWRONEK	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,4,6,8,10 and 14-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,4,6,8,10 and 14-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 July 2008* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

Claims 3, 4, 6, 8, 10, 14, 15, and 16 are pending.

Claims 1-2, 5, 7, 9, and 11-13 are cancelled.

Claims 3, 4, 6, 8, 10, 14, 15, and 16 have been examined.

Claims 3, 4, 6, 8, 10, 14, 15, and 16 are rejected.

Priority

This application is the national stage of PCT/EP04/51084 filed on 10 June 2004 and claims the benefit of US provisional Application No. 60/478,780 filed on 16 June 2003 and European Patent Office application No. 03101687.6 on 10 June 2003.

Drawings

The replacement drawings submitted on 29 July 2008 are acceptable. The objection to the drawings is withdrawn.

Specification

Response to Arguments

Applicant's arguments, see Remarks p. 13, filed 29 July 2008, with respect to the objection to the specification relating to browser executable code have been fully considered and are persuasive. The objection to the specification has been withdrawn. However, upon further consideration, it is noted that in the amendment to the specification, filed 29 July 2008, "Stanford university" should be capitalized as "Stanford University".

The objection to the abstract has been withdrawn in view of the new abstract filed 29 July 2008.

Claim Objections

Response to Arguments

Applicant's arguments, see Remarks p. 13, filed 29 July 2008, with respect to the objection to claims 3, 4,6, 7, 9, and 11 have been fully considered and are persuasive. The objection to claims 3, 4, 6, 7, 9, and 11 has been withdrawn in view of the amendments to the claims.

Claims 3, 4, and 8 are objected to because of the following informalities:

Claim 8 depends, in the last line, from claim 1 which is now cancelled and is improperly dependent. For the purpose of examination, claim 8 is interpreted to be dependent from claim 3;

Claim 3 recites "calculating average pFR for all mutations" at line 29, which is grammatically imprecise, either the article "an" is missing before the term average or the term "pFR" should be plural to agree with the term mutations;

Claim 3 at line 37 recites "approximates to" the term "to" should be removed;

Claim 4 at line 44 the term "to" in the phrase "approximates to" should be removed;

Claim 6 recites two steps labeled (a);

In claim 6, the term "center" is misspelled in lines 38 and 46; and

In claim 6 line 50, the term "phenotypes" should be "phenotype".

Appropriate correction is required.

Claim Rejections - 35 USC § 101

Response to Arguments

Applicant's arguments, see Remarks p 13-14, filed 29 July 2008, with respect to the rejection of claims 1, 2, 5, 7, 9, 11, and 13 as non-statutory under 35 USC 101 have been fully considered and are persuasive. The rejection of claims 1, 2, 5, 7, 9, 11, and 13 has been withdrawn in view of the cancellation of the claims.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 16 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claim 16 is directed to a computer program product comprising a computer readable storage medium and a computer program mechanism. The specification doe not provide a definition for a "computer program mechanism". The term is being interpreted as broadly as reasonable to encompass both computer-executable forms of programs and as program code or listing. As a program code or listing, not limited to be an executable program or listing, it is interpreted to be nonfunctional descriptive material. A computer readable medium comprising

nonfunctional descriptive material is non-statutory. See MPEP 2106, Section II. As the claim encompasses a nonstatutory embodiment, it is rejected herein.

Claim 16 is also non-statutory with respect to the computer readable medium. The specification does not indicate the types of medium that are envisioned. Giving the computer readable medium its broadest reasonable interpretation, the medium reads on both media such as optical discs and as media such as carrier signals. Carrier signals are a natural phenomenon and are non-statutory. Thus the claim is directed to non-statutory subject matter.

Claims 3, 4, 6, 8, 10, 14, 15, and 16 are drawn to a process, apparatus that performs the process and a computer program. A statutory process must include a step of a physical transformation, or produce a useful, concrete, and tangible result (State Street Bank & Trust Co. v. Signature Financial Group Inc. CAFC 47 USPQ2d 1596 (1998), AT&T Corp. v. Excel Communications Inc. (CAFC 50 USPQ2d 1447 (1999)). The instant claims do not result in a physical transformation, thus the Examiner must determine if the instant claims include a useful, concrete, and tangible result.

As noted in State Street Bank & Trust Co. v. Signature Financial Group Inc. CAFC 47 USPQ2d 1596 (1998) below, the statutory category of the claimed subject matter is not relevant to a determination of whether the claimed subject matter produces a useful, concrete, and tangible result:

> The question of whether a claim encompasses statutory subject matter should not focus on which of the four categories of subject matter a claim is directed to -- process, machine, manufacture, or composition of matter--but rather on the essential characteristics of the subject matter, in particular, its practical utility. Section 101 specifies that statutory subject matter must also satisfy the other "conditions and requirements" of Title 35, including novelty, nonobviousness, and adequacy of disclosure and notice. See *In re Warmerdam*, 33 F.3d 1354, 1359, 31 USPQ2d 1754, 1757-58 (Fed. Cir. 1994). For purpose of our analysis, as noted above, claim 1 is directed to a machine programmed with the Hub and Spoke software and admittedly produces a "useful, concrete, and tangible result." *Alappat*, 33 F.3d at 1544, 31 USPQ2d at 1557. This renders it statutory subject matter, even if the useful result is expressed in numbers, such as price, profit, percentage, cost, or loss.

In determining if the claimed subject matter produces a useful, concrete, and tangible result, the Examiner must determine each standard individually. For a claim to be "useful," the claim must produce a result that is specific, and substantial. For a claim to be "concrete," the process must have a result that is reproducible. For a claim to be "tangible," the process must produce a real world result. Furthermore, the claim must be limited only to statutory embodiments.

Claims 3, 4, 6, 8, 10, 14, 15, and 16 do not require production of a tangible result in a form that is useful to the user of the process or apparatus. The process, apparatus and program are directed to the quantification of at least a mutation to a drug resistance phenotype of HIV by performing a linear regression on matched genotype-phenotype data. The process or apparatus do not return a tangible result to the practitioner of the process or apparatus. A tangible result requires that the claim must set forth a practical application to produce a real-world result. This rejection could be overcome by amendment of the claims to recite that a result of the process is outputted to a display, or to a user, or in a graphical format, or in a user readable format, or by including a result that is a physical transformation. The applicants are cautioned against introduction of new matter in an amendment.

Claims 3, 4, 6, 8, and 10 are directed to a process for quantitating the individual contribution of a mutation to a drug resistance phenotype. The following analysis is taken from the guidance provided in the MPEP at 2104.IV, "Determine Whether the Claimed Invention Complies with 35 USC101". The claims are directed to processes. Here the claims are directed to the abstract ideas of linear regression analysis,

statistical correlation analysis and probability predictions. The processes do not recite a physical transformation of matter from one state to another. Giving the claims the broadest reasonable interpretation, the claims read on mental steps. In *Comiskey* (*In re Comiskey*, 84 USPQ2d 1670) the court established that "the application of human intelligence to the solution of practical problems is not and of itself patentable" (at 1680). In *Comiskey*, the court stated explicitly "mental processes - or processes of human thinking - standing alone are not patentable even if they have a practical application" (at 1679). The court in *Comiskey* stated, "Following the lead of the Supreme Court, this court and our predecessor court have refused to find processes patentable when they merely claimed a mental process standing alone and untied to another category of statutory subject matter even when a practical application was claimed" (at 1680). In the instant claims, the process is not tied to a class of statutory invention.

The court in *Comiskey*, also stated "the court rejected the notion that mere recitation of a practical application of an abstract idea makes it patentable, concluding that '[a] competent draftsman could attach some form of post-solution activity to almost any mathematical formula'" citing *Flook* (437 U.S. at 586, 590). Applicant is encouraged to consider the recent BPAI informative decisions *Exparte Langemyr* (No. 2008-1495 (28 May 2008)) and *In Re Biliski* (No. 2007-1130 (30 October 2008)) for further clarification of the above grounds of rejection.

Response to Arguments

Applicant's arguments filed 29 July 2008 have been fully considered but they are not persuasive. Applicant argues that the amendment to the claims reciting "thereby

quantitating the individual contribution of a mutation to drug resistance phenotype exhibited by HIV" overcomes the rejection under 35 USC 101. The argument is not persuasive because the claims do not recite a tangible output.

Claim Rejections - 35 USC § 112

Response to Arguments

Applicant's arguments, see Remarks p. 14, filed 29 July 2008, with respect to the rejections of claims 1-11 and 13-16 under 35 USC 112, second paragraph have been fully considered and are persuasive. The rejection of claims 1-11 and 13-16 has been withdrawn in view of applicants' amendment to the claims. However, upon further consideration new grounds of rejection are made under 35 USC 112, second paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 4, 6, 8, 10, and 14-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3 and 4 are indefinite with respect to the extremes, either minimum or maximum, as recited in lines 31-33 and in lines 28-29 and 37-38, respectively. The claim does not clearly indicate what relation the extremes have with respect to the claimed subject matter (i.e. extremes of WHAT?), which makes the metes and bounds

of the claim indefinite. Claims 8, 10, and 14-16 are also rejected because they depend from claim 3, and thus contain the above issues due to said dependence.

Claim 3 is indefinite with respect to the step d in line 36-38. The metes and bounds of the step are unclear for two reasons. First, the use of a step a and b that is followed by a step d suggest that a step c is performed. The claim however does not recite a step c. Second, the claim recites in step d "stop when said selected mutation in step ii has an average pFR that approximates the global average." Since the selected mutation is removed from the data set in step b, it is unclear which mutation is, in fact, intended to approximate the global average.

Claim 4 is indefinite with respect to the calculation step of lines 26-27 and 35-36. The metes and bounds of claim 4 are rendered indefinite by the calculating step of lines 26-27 and 35-36 because a singular correlation coefficient is claimed between a plurality of mutations or residue, respectively. It is not clear from the claim if an average correlation coefficient for all mutations is calculated or if a pairwise comparison is performed. If a pairwise comparison is performed, the claim does not provide clear indication of the process for a single correlation coefficient that is not an average and which is formed from multiple pairwise comparisons.

Claim 4 is indefinite with respect to "the pFR" recited in line 27. The metes and bounds are indefinite because it is unclear which pFR is used to determine the correlation coefficient.

Claim 4 is indefinite with respect to the step for determining a residue that is a pFR minus a modeled prediction as recited in lines 33-34. The metes and bounds of the

residue determining step are indefinite because the claim recites several different pFR values, each of which is a modeled prediction. The multiple pFR values make the claim unclear regarding the calculation or determination of the residue in lines 33-34, as the practitioner does not know which of the plurality of pFR values are to be used to calculate the residue.

Claim 6 is indefinite with respect to the step of "looking at the prediction from the model and apply either" in lines 31-47. The metes and bounds of the step are unclear because the claim recites either at line 31 but does not provide any alternatives. Line 32 recites the phrase "when case '<'-censor:". The metes and bounds of the phrase are unclear because phrase does not indicate not indicate any particular action. One does not know what "when case '<'-censor:" means or what step is performed. Similarly, line 40 recites the phrase "when case '>'-censor:". The metes and bounds of the phrase are unclear because phrase does not indicate not indicate any particular action. One does not know what "when case '>'-censor:" means or what step is performed. It is further unclear if substeps (i), (ii), and (iii) in lines 33-39 and lines 41-47 are all performed, performed in part, or are optional. In addition, the claim provides no indication of how the substeps (i), (ii), and (iii) in lines 33-39 and lines 41-47 limit the claim The lack of punctuation in lines 31-47, makes the claim indefinite because one can not determine the scope of the claimed elements. It is unclear if the parenthetical phrase "center of gravity of half Gaussian distribution" is a limitation of the claim 6 in lines 33 and 41. The recitation of the prediction P is indefinite. The metes and bounds of "the prediction P" is

indefinite because it is unclear which of the predictions, either pFR or the linear regression model without censored values, is being "looked at" in step c at line 31.

The using step of line 29 in claim 6 is indefinite with respect to the origin of the phenotypic value V_0. The metes and bounds of the censor is indefinite because lines 1-27, the steps preceding step b do not employ, indicate the origin, or determination of the phenotypic value V_0. While the dataset of matching phenotypes and genotypes is claimed, it is unclear what the relation of the phenotype value V_0 is to the dataset of matching phenotypes and genotypes.

The reiteration step e at line 51 in claim 6 is indefinite. The metes and bounds of step e at line 51 of claim 6 are indefinite because the step does not distinctly indicate which steps are to be reiterated or which part of step is subject to reiteration.

It is unclear in claim 6, if the censored value of line 24 is a genotype, phenotype or some other value.

Claim Rejections - 35 USC § 103

Response to Arguments

The rejection of 1, 2, 7-11, 13-15, and 16 has been withdrawn in view of the cancellation of claims 1-2, 7, 9, 11, and 13.

The rejection of claim 5 has been withdrawn in view of the cancellation of claim 5.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 3, 8, 10, and 14-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Servais et al. (Antiviral Therapy, Vol. 6, p. 239-248, 2002), in view of Carter et al. (US PG PUB 2004/0138826), and in view of Kempf et al.(Journal of Virology, vol. 75, no. 16, p. 7462-7469, August 2001).

The claims are drawn to a method, system and program for quantifying the contributions of mutations to drug resistance of an HIV strain by performing a linear

regression analysis on matching genotype-phenotype data to generate a log fold resistance where the log fold resistance can be expressed as the sum of the mutation contributions; and the average log resistance is determined for the set to which the log resistance for each mutant is compared, where mutants that are close to the average are retained and those distant to the average are removed from the set. In some embodiments, the method further comprises obtaining a genetic sequence of an HIV strain and identifying a pattern of mutations that are associated with resistance. In some embodiments, correlations are removed from the dataset using an algorithm that tracks the predicted response as mutations are removed from the data set. In some embodiments, the resistance of HIV strains is tested in a patient and is used to select the drug with the lowest predicted fold resistance.

Servais et al. shows a method of quantifying the contributions of mutations to drug resistance of an HIV strain by performing a linear regression analysis on matching genotype-phenotype data to generate a log fold resistance. Servais et al. shows that a linear mixed effects regression analysis was performed to measure the association between the quantitative predictor variable (the mutations) and the longitudinal data (the resistance phenotype) (p. 241, col. 2). Servais et al. further shows that through the use multiple regressions of the genotype-phenotype data, the additive nature of individual mutation is identified (p. 242, col. 1-col. 2). In figure 2, Servais et al. shows results of the correlation between mutational patterns of HIV protease inhibitors and log fold resistance. Servais et al. shows an embodiment in which the genetic sequence of an HIV strain is obtained via sequencing (p. 240, col. 2). Servais et al. shows an

embodiment in which a pattern of mutations is identified that is correlated with a resistance phenotype (p. 240, col. 1-2). Servais et al. shows an embodiment in which the resistance of HIV strains is tested in a patient and is used to select the drug with the lowest predicted fold resistance (p. 246, col. 1).

Servais et al. does not show the equation: $pFR = \beta_A M_A + \beta_B M_B + \beta_n M_n + \varepsilon$.

Carter et al. shows a method of statistical analysis of interactions among mixtures of agents. Carter et al. shows that interaction between agents to produce a particular response can be modeled statistically with the additivity equation $\mu = \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_{12} + \beta_0$ [0014-0021]. Carter et al. shows the equation can be used to determine the contributions of the agents in a mixture of agents as synergistic, antagonistic or no interaction [0027]. Carter et al. shows that agents can be something other than a chemical substance [0093]. Carter et al. suggest that agents can be a condition, characteristic, or phenomena that an individual is exposed to. Mutations fit the criterion of a characteristic insofar as mutations are characteristics that define the activity a given protein, thus the term agent reads on the term mutation. Carter et al. describes that the methods and equation are not limited to two components. Carter et al. shows the general form of the equation suitable to any number of components or agents [0109]. Carter et al. shows the β variable represents synergism or antagonism [0024]. The variable x in the equation of [0014] is the concentration of agent in the mixture an represents the degree to which the agent is present in the mixture [0013]. Carter et al. shows this more clearly by normalizing the sum of the degree of an agent's presence to 1 [0111]. The β_0 term of the equation is an unknown intercept which Carter

et al. shows represents the difference between the model and the experimentally determined data [0096]. Carter et al. shows that the additivity equation is equivalent to a simple linear regression [0679]. Carter et al. shows an embodiment in which correlations are removed from the dataset using an algorithm that tracks the predicted response as mutations are removed from the data set [0040-43]. Carter et al. shows an embodiment in which the method is applied iteratively in cases where small data sets are used [0101].

Servias et al. in view of Carter do not explicitly show a process by which the log resistance of a mutation is compared to the average resistance of the set mutations and is removed if it is significantly dissimilar to the average for the set.

Kempf et al. describes a statistical process for identifying mutations in the HIV virus that are linked to the drug resistance phenotypes. Similar to the claimed process, Kempf et al. shows that mutants having a p value beyond a threshold for statistical significance are removed (p. 7463, col. 1). Kempf et al. shows that the statistical comparison occurred between mean resistance for the set and the individual strains (p. 7463, col. 1). On the basis of the statistical comparison Kempf et al. was able to quantitate the individual contributions of the mutations to the drug resistance phenotype of HIV (p. 7464, col. 2). Kempf et al. shows that the statistical comparison methods were used successfully to identify mutation in HIV that correlate with increased resistance to the protease inhibitor, lopinavir (p. 7467, col. 1). Kempf et al. shows the statistical method has the benefit of being useful for estimating the potential for reduced

susceptibility to lopinavir in patients failing therapy with other protease inhibitors (p. 7467, col. 2).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the linear regression analysis of genotype-phenotype HIV strain drug resistance data of Servais et al. with the statistical regression analysis of mixtures of agents taught by Carter et al. because the substitution of the different regression analysis methods for one another would have yielded predictable results. One would have had a reasonable expectation of success in substituting linear regression of Servais et al. with the linear regression of Carter et al. because both Carter et al. and Servais et al. successfully applying linear regressions to data. It would have been further obvious to modify the linear regression analysis of genotype-phenotype HIV strain drug resistance data and the statistical regression analysis of mixtures of agents made obvious by Servais et al in view of Carter et al. with the statistical comparisons of Kempf et al. because Kempf et al. shows the statistical method has the benefit of being useful for estimating the potential for reduced susceptibility to lopinavir in patients failing therapy with other protease inhibitors.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Servais et al. (Antiviral Therapy, Vol. 6, p. 239-248, 2002), in view of Carter et al. (US PG PUB 2004/0138826), and in view of Michelson et al. (The Biostatistics Cookbook, Kluwer Academic Publishers, 1996).

The claim is drawn to a method for quantifying the contributions of mutations to drug resistance of an HIV strain by performing a linear regression analysis on matching genotype-phenotype data to generate a log fold resistance where the log fold resistance can be expressed as the sum of the mutation contributions; and the average log resistance is determined for the set to which the log resistance for each mutant is compared, where mutants that are close to the average are retained and those distant to the average are removed from the set. In some embodiments, the method further comprises obtaining a genetic sequence of an HIV strain and identifying a pattern of mutations that are associated with resistance. In some embodiments, correlations are removed from the dataset using an algorithm that tracks the predicted response as mutations are removed from the data set. In some embodiments, the resistance of HIV strains is tested in a patient and is used to select the drug with the lowest predicted fold resistance.

Servais et al. shows a method of quantifying the contributions of mutations to drug resistance of an HIV strain by performing a linear regression analysis on matching genotype-phenotype data to generate a log fold resistance. Servais et al. shows that a linear mixed effects regression analysis was performed to measure the association between the quantitative predictor variable (the mutations) and the longitudinal data (the resistance phenotype) (p. 241, col. 2). Servais et al. further shows that through the use multiple regressions of the genotype-phenotype data, the additive nature of individual mutation is identified (p. 242, col. 1-col. 2). In figure 2, Servais et al. shows results of the correlation between mutational patterns of HIV protease inhibitors and log fold

resistance. Servais et al. shows an embodiment in which the genetic sequence of an HIV strain is obtained via sequencing (p. 240, col. 2). Servais et al. shows an embodiment in which a pattern of mutations is identified that is correlated with a resistance phenotype (p. 240, col. 1-2). Servais et al. shows an embodiment in which the resistance of HIV strains is tested in a patient and is used to select the drug with the lowest predicted fold resistance (p. 246, col. 1). Servais et al shows the determination of multiple correlation coefficients (p. 242, col. 2). Servais et al. shows in table 3 that the predictive value increases as more associated mutations are added to the model. In table 3 Servais et al. shows that by performing step wise multiple regressions, multiple correlation coefficients could be determined. Servais et al shows in table 3 that 54V always associate with 82A and explained 49% of the resistance. The correlation between 82A, 54V and 10I explained an additional 8%. The results of Servais et al suggests that model can be improved by adding correlated mutations.

Servais et al. does not show the equation: $pFR = \beta_A M_A + \beta_B M_B + \beta_n M_n + \varepsilon$.

Carter et al. shows a method of statistical analysis of interactions among mixtures of agents. Carter et al. shows that interaction between agents to produce a particular response can be modeled statistically with the additivity equation $\mu = \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_{12} + \beta_0$ [0014-0021]. Carter et al. shows the equation can be used to determine the contributions of the agents in a mixture of agents as synergistic, antagonistic or no interaction [0027]. Carter et al. shows that agents can be something other than a chemical substance [0093]. Carter et al. suggest that agents can be a condition, characteristic, or phenomena that an individual is exposed to. Mutations fit

the criterion of a characteristic insofar as mutations are characteristics that define the activity a given protein, thus the term agent reads on the term mutation. Carter et al. describes that the methods and equation are not limited to two components. Carter et al. shows the general form of the equation suitable to any number of components or agents [0109]. Carter et al. shows the β variable represents synergism or antagonism [0024]. The variable x in the equation of [0014] is the concentration of agent in the mixture an represents the degree to which the agent is present in the mixture [0013]. Carter et al. shows this more clearly by normalizing the sum of the degree of an agent's presence to 1 [0111]. The β_0 term of the equation is an unknown intercept which Carter et al. shows represents the difference between the model and the experimentally determined data, reading on a residue [0096]. Carter et al. shows that the additivity equation is equivalent to a simple linear regression [0679]. Carter et al. shows an embodiment in which correlations are removed from the dataset using an algorithm that tracks the predicted response as mutations are removed from the data set [0040-43]. Carter et al. shows an embodiment in which the method is applied iteratively in cases where small data sets are used [0101].

Michelson et al. shows that the correlation coefficient is a measure of the degree of association between two variables (p. 122). Michelson et al. shows variables that are strongly associated, have correlation coefficients that approach 1, whereas variables that are completely not-associated have correlation coefficients that approach 0 (p. 123).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the linear regression analysis of genotype-phenotype HIV strain drug resistance data of Servais et al. with the statistical regression analysis of mixtures of agents, as taught by Carter et al., because the substitution of the different regression analysis methods for one another would have yielded predictable results. One would have had a reasonable expectation of success in substituting linear regression of Servais et al. with the linear regression of Carter et al. because both Carter et al. and Servais et al. successfully applying linear regressions to data. It would have been further obvious to modify the linear regression analysis of genotype-phenotype HIV strain drug resistance data and the statistical regression analysis of mixtures of agents of Servias et al in view of Carter et al. with the determination of correlation coefficients because Michelson et al. shows that the correlation coefficient is measure of the statistical association between variables which has the benefit of indicating that the variables linked. It would have been further obvious to use the correlation coefficient of Michelson et al. to identify mutations that are statistically associated and iteratively add the variables having the highest correlation to the model of resistance as taught by Servais et al. because Servais et al suggests that through the use of correlation coefficients and stepwise linear regressions an improvement in predictive value can be achieved. It would have been further obvious to modify the method of predicting the contribution of mutation to resistance based on the correlation coefficients of the mutations and the measure of resistance because all the claimed elements were known, in the prior art, and one skilled in the art could have combined

the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art at the time of the invention.

Conclusion

None of the claims are currently in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KARLHEINZ R. SKOWRONEK whose telephone number is (571) 272-9047. The examiner can normally be reached on 8:00am-5:00pm Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on (571) 272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Examiner, Art Unit 1631

18 November 2008

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